

FDA Approval of Aptivus (tipranavir)

On June 22, 2005, the US Food and Drug Administration (FDA) granted accelerated approval of APTIVUS (tipranavir), a protease inhibitor. APTIVUS, co-administered with 200 mg of ritonavir, is indicated for use as part of combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

FDA reviewed and approved APTIVUS within a six month time frame.

Clinical Study Results

The approval of APTIVUS/ritonavir is based on analyses of plasma HIV-1 RNA levels in two controlled phase III studies of APTIVUS/ritonavir of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV1 replication despite ongoing antiretroviral therapy. The results of the two phase III studies showed a statistically significant greater percentage of HIV-positive patients taking APTIVUS/ritonavir achieved treatment response versus the comparator group (40% vs. 18%). Treatment response was defined as a confirmed $1 \log_{10}$ or greater decrease in HIV RNA from baseline.

Dosage and Administration

The approved dose of APTIVUS is 500 mg taken with 200 mg of ritonavir, twice daily with food. APTIVUS must be co-administered with 200 mg of ritonavir to exert its therapeutic effect. Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect. Taking the drug with food improves absorption.

Usage Information:

The following points should be considered when initiating therapy with APTIVUS/ritonavir:

- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response.
- Genotypic or phenotypic resistance testing and/or treatment history should guide the use of APTIVUS/ritonavir. The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir.
- Because APTIVUS can cause serious liver toxicity, liver function tests should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment
- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, Hepatitis B or C co-infection, or other underlying hepatic (liver) impairment
- APTIVUS used with low-dose ritonavir has many drug interactions. Therefore, patients should report to their health care provider the use of any other prescription, non-prescription medication or herbal products, particularly St. John's Wort. Certain medicines such as antiarrhythmics (medicines that treat irregular heart beats), antihistamines, ergot derivatives (found in some medicines to treat migraine headaches), medicines that speed up the digestive tract, herbal products, some medicines that lower cholesterol levels, and medicines to treat mental problems should never be given with APTIVUS plus ritonavir because serious side effects could occur.

Patients receiving estrogen-based birth control pills or patches should be instructed that additional or alternative forms of birth control should be used when taking APTIVUS.

The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use.

- The risk-benefit of APTIVUS/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.
- There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

Safety Information:

The most commonly ($\geq 3\%$) reported adverse reactions were diarrhea, nausea, fatigue, headache and vomiting. The most commonly reported laboratory abnormalities were elevated liver enzymes, cholesterol and triglycerides.

Hepatotoxicity

The APTIVUS label includes a Black Box warning regarding hepatotoxicity. Specifically, APTIVUS co-administered with low dose ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with APTIVUS/ritonavir, and frequently throughout the duration of treatment.

In addition, APTIVUS is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency.

Sulfa Allergy

APTIVUS should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide component. The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir is unknown.

Rash

Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving APTIVUS/ritonavir. In Phase 2 and 3 trials rash was observed in 14% of females and in 8-10% of males receiving APTIVUS/ritonavir. Additionally, in one drug interaction trial in healthy female volunteers given a single dose of ethinyl estradiol (a hormonal contraceptive) followed by APTIVUS/ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus (itching) has been reported in both men and women receiving APTIVUS/ritonavir.

Ongoing Clinical Trials

Boehringer Ingelheim agreed to continue to evaluate the safety and efficacy of APTIVUS in the following patient populations:

- Pediatric patients
- Treatment-naïve adults
- HIV-positive women
- Hepatitis co-infected patients

Additional drug-drug interaction studies are planned.

Currently there are seven other protease inhibitors approved by FDA for the treatment of HIV infection. These medications work at the final stages of viral replication and attempt to prevent HIV from making new copies of itself by interfering with the HIV protease enzyme. As a result, the new copies of HIV are not able to infect new cells.

The manufacturer of APTIVUS is Boehringer Ingelheim Pharmaceuticals.

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An archive of past list serve announcements is available on the FDA web site at
<http://www.fda.gov/oashi/aids/listserve/archive.html>